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Is Inhaled Arsenic Carcinogenic for Sites Other Than the Lung

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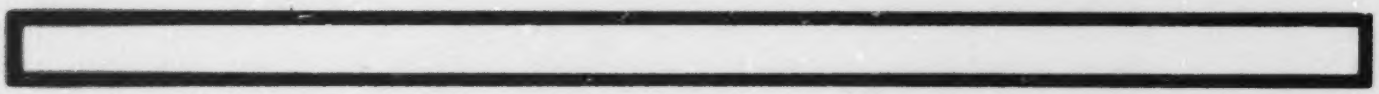

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16. ABSTRACT

The carcinogenic risk from inhaled arsenic for sites other than the lung is discussed. Data from persons ingesting arsenic as well as from persons inhaling arsenic are considered in arriving at the conclusions. In the past, lung cancer has generally been assumed to be the only cancer risk due to arsenic exposure via inhalation. The evidence suggests, however, that inhalation exposure to arsenic increases the risk of gastrointestinal, urinary tract, and skin cancer in addition to lung cancer. A lifetime gastrointestinal cancer risk from a lifetime exposure of 1 ug/m^3 of ambient arsenic is estimated to be 4.3×10^{-4}.

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The views expressed in this paper are those of the authors and do not necessarily reflect the views and policies of the U.S. Environmental Protection Agency.

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1. INTRODUCTION

In March 1984 the U.S. Environmental Protection Agency (EPA) released its Health Assessment Document on Arsenic (U.S. EPA, 1984a). In that report numerous epidemiologic studies of the carcinogenic risk of inhaled and ingested arsenic were reviewed. The lung, not surprisingly, has consistently proven to be a target organ for the carcinogenic effects from inhaled arsenic. While some of the epidemiologic studies of persons exposed to arsenic via inhalation noted excess risks of cancer for organs or systems other than the lung, these results have been given little attention.

Recently, Chen and Chen (1988) presented an integrated quantitative risk assessment of inorganic arsenic and demonstrated that the relative magnitudes of the potencies of internal cancers (lung, liver, kidney, and bladder) induced by arsenic in the drinking water are consistent with the relative magnitudes of the tissue concentration of arsenic in each of these organs. They further demonstrated that the risk of lung cancer induced by arsenic in the drinking water is consistent with the risk observed in the occupational setting. On these bases they hypothesized that arsenic smelter workers may have an elevated risk of cancer for sites other than the lung.

The purpose of this paper is to discuss the

evidence for cancer risk at sites other than the lung resulting from arsenic inhalation and to present a dose-response assessment for such data. In discussing the evidence we will use the data by the ingestion route of exposure as well as that from the inhalation route in arriving at our conclusions. We will also discuss the ramifications that the arsenic data has for the carcinogen risk assessment of other substances.

2. EVIDENCE OF THE CARCINOGENIC RISK OF INHALED ARSENIC AT SITES OTHER THAN THE LUNG

Numerous studies have reported an excess risk of lung cancer among smelter worker populations (Lee-Feldstein, 1983; Enterline and Marsh, 1982; Rencher et al., 1977; Tokudome and Kuratsune, 1976; Jarup et al., 1988) and workers engaged in arsenical pesticide manufacture (Mabuchi et al., 1979; Hill and Faning, 1948; Ott et al., 1974). While little attention has been paid to the association of inhaled arsenic with an excess risk of cancer of organs other than the lung, we believe the data deserve a closer examination.

Lee-Feldstein (1983) found a significant excess of digestive tract as well as respiratory cancer mortality among 8045 arsenic-exposed smelter workers at the Anaconda smelter in Anaconda, Montana (SMR = 125, 167 observed deaths, 133.58 expected deaths, $p < 0.05$). She also found that men employed prior to 1925 (when

exposure to arsenic was most intense) and who worked 25 years or more experienced twice the expected number of bladder cancer deaths (SMR = 200, 13 observed, 6.5 expected, $p < 0.05$).

Wall (1980) found a significant excess of stomach cancer mortality and mortality from tumors of the brain and nervous system ($p < 0.05$) as well as an excess of respiratory cancer mortality among a group of Swedish smelter workers. The author also found a dose response for stomach cancer mortality by duration of exposure.

Tokudome and Kuratsune (1976) found an excess of both liver cancer mortality (SMR = 337, 11 observed deaths, 3.26 expected deaths, $p < 0.05$) and colon cancer mortality (SMR = 508, 3 observed deaths, 0.59 expected deaths, $p < 0.05$) as well as lung cancer mortality among a group of arsenic-exposed copper smelter workers in Saganoseki-machi, Japan.

Enterline and Marsh (1982) found a slight excess of digestive tract cancer mortality among a cohort of 2802 arsenic-exposed workers at the ASARCO smelter in Tacoma, Washington (SMR = 109, 65 observed deaths, 59.7 expected deaths, $p > 0.05$). The SMRs were somewhat higher for stomach, colon, and rectal cancer (122, 120, and 122, respectively) although none were statistically significant. The SMR for colon cancer for those first employed before 1930 was statistically significant

however (SMR = 208.5, 12 observed deaths, 5.75 expected deaths, $p < 0.05$). This excess in the period before 1930 is probably related to the fact that workers at the smelter began using respirators in the 1940s which were found to be 99% effective. Enterline and Marsh also reported an excess of kidney cancer mortality (SMR = 133), but this excess was not statistically significant ($p > 0.05$). Here again, however, the SMR for workers first employed before 1930 and thus before respirators were employed was higher (SMR = 201) although still not statistically significant ($p > 0.05$).

A proportional mortality study of sheep dip manufacturing workers (Hill and Faning 1948) in which the study population was exposed to arsenic primarily via inhalation reported an excess of skin cancer mortality. Limitations of proportional mortality studies are well known (Rothman 1986); nevertheless, the results are consistent with the numerous studies of persons ingesting arsenic and developing skin cancer (U.S. EPA 1988). Furthermore, the results of the proportional mortality study are supported by the results of the subsequent clinical and environmental investigation of the sheep dip factory workers and the factory, respectively, by Perry et al. (1948). Perry et al. found that the workers exposed to arsenic dust had a higher content of arsenic in their hair, excreted more

arsenic in their urine, and had a higher prevalence of hyperpigmentation and hyperkeratinization than controls. Hyperpigmentation and hyperkeratinization are hallmarks of arsenic exposure via ingestion and such arsenic-induced hyperkeratinization may be precancerous (U.S. EPA 1988).

Ott et al. (1974) reported that workers exposed to arsenic in a pesticide manufacturing plant had a significant excess risk of mortality from neoplasms of the lymphatic and hematopoietic tissues other than leukemia (SMR = 385, 5 observed deaths, 1.3 expected deaths, $p < 0.01$). Axelson et al. (1978) reported that cases of leukemia and myeloma were significantly more likely to be exposed to arsenic than controls ($p < 0.02$).

A conclusion of an excess cancer risk from arsenic inhalation for sites other than the lung is consistent with the results of studies of persons exposed to arsenic by ingestion. Chen et al. (1985) found that SMRs for cancer of the lung, bladder, kidney, skin, liver, and colon were significantly increased in an area of Taiwan where there was endemic arsenic contamination of the water supply. In a follow-up case-control study in the arsenic endemic area, Chen et al. (1986) found an association of arsenic ingestion with bladder, lung, and liver cancer. In both of these studies and a subsequent

SMR study (Chen et al. 1988), the authors found evidence of a cancer dose response to arsenic.

In addition to the studies by Chen et al., there are numerous case reports of persons ingesting arsenic and developing cancer of the internal organs. Fierz (1965), Regelson et al. (1968), Lander et al. (1975), Popper et al. (1978), Falk et al. (1981), and Roat et al. (1982) reported cases of persons who had ingested arsenical medicinals and developed liver cancer. Sommers and McManus (1953) and Nagy et al. (1980) reported cases of bladder cancer that had been chronically exposed to arsenic by ingestion. Nurse (1978) reported on a patient who developed kidney cancer after being treated with an arsenical medicinal.

Studies and case reports supporting an association of arsenic exposure with an excess risk of cancer at sites other than the lung are summarized in Table 1.

Table 1. Epidemiologic Studies and Case Reports Supporting an Association of Arsenic Exposure and Excess Risk of Cancer at Sites Other Than The Lung By Route of Exposure and By Body Organ or System

Neoplasms of Organ and/or System:	Route of Exposure Inhalation	Ingestion
Digestive Organs & Peritoneum (ICD 150-159)	Lee-Feldstein (1983)	
Stomach (ICD 151)	Wall (1980)	
Colon (ICD 153)	Tokudome and Kuratsune (1976) Enterline and Marsh (1982)	Chen et al. (1985, 1988)
Liver (ICD 155)	Tokudome and Kuratsune (1976)	Chen et al. (1985, 1986, 1988) Roat et al. (1982) Falk et al. (1981) Popper et al. (1978) Lander et al. (1975) Regelson et al. (1968) Fierz (1965)
Genitourinary System (ICD 179-189)		
Bladder (ICD 188)	Lee-Feldstein (1983)	Chen et al. (1985, 1986, 1988) Nagy et al. (1980) Sommers and McManus (1953)
Kidney (ICD 189)	Enterline and Marsh (1982)	Chen et al. (1985, 1988) Nurse (1978)

Table 1. Continued

Neoplasms of (Organ and/or System):	Route of Exposure Inhalation	Ingestion
Skin[a] (ICD 173)	Hill and Faning (1948)	Chen et al. (1985, 1988) Cebrian et al. (1983) Tseng (1977) Tseng et al. (1968) Zaldivar and Guiller (1977) Fierz (1965) Bergoglio (1964) Sommers and McManus (1953)
Lymphatic and Hematopoietic Tissue (ICD 200-208)		
Lymphatic and hematopoietic and tissue other than leukemia (ICD 200-203)	Ott et al. (1974)	
Myeloma & Leukemia (ICD 204-209)	Axelson et al. (1978)	
Brain and Nervous System (ICD 191-192)	Wall (1980)	

[a]The studies demonstrating an association of arsenic ingestion and skin cancer are too numerous to mention here. Refer to U.S. EPA (1988) for a complete description of studies and reports of skin cancer induced by arsenic.

3. DOSE-RESPONSE ANALYSIS

As can be seen from Table 1, numerous studies support an association of inhaled arsenic with an excess risk of cancer of systems other than the respiratory system. The evidence appears to be the strongest for an association of arsenic exposure with cancer of the gastrointestinal and urinary systems.

The largest cohort study of persons exposed to arsenic by inhalation is that by Lee-Feldstein (1983). Dr. Lee-Feldstein has provided us with an updated data tape of her study which we have used for a dose-response assessment of inhaled arsenic and gastrointestinal cancer, the results of which we present here. The method used is similar to that used by the EPA to estimate a unit risk for lung cancer from inhaled hexavalent chromium (U.S. EPA 1984b). The only significant difference is that for this assessment we counted person-years of observation beginning at the end rather than at the beginning of employment. For dose-response assessment this approach better characterizes individual exposure as noted by Enterline (1976).

From the updated Lee-Feldstein data, we estimated the lifetime gastrointestinal and respiratory cancer risk due to 1 ug/m^3 of arsenic in air to be 4.3×10^{-4} and 1.7×10^{-3}, respectively. We note that the unit-risk estimate for respiratory cancer risk presented here

is almost identical to that estimated by the U.S. EPA (1984a) using the Lee-Feldstein (1983) data and counting person-years since the beginning of employment.

We also note that the unit-risk estimate for gastrointestinal cancer presented here is not insignificant when compared to the unit cancer risk estimates that the EPA has calculated for other chemicals. The inhalation unit-risk estimate for arsenic for gastrointestinal cancer alone is higher than the inhalation unit-risk estimates calculated by the EPA for several chemicals including acrylonitrile, benzene, trichloroethylene, perchloroethylene, vinyl chloride, and ethylene oxide.

4. DISCUSSION

It is well established that exposure to arsenic is causally associated with excess risks of cancer of the respiratory system and skin (U.S. EPA 1984a, 1988; Health and Safety Executive 1986; International Programme on Chemical Safety 1981). We believe that sufficient information exists to conclude that exposure to arsenic is also associated with excess risks of cancer of the gastrointestinal system, including the stomach, colon, and liver, and the urinary system. Excess risks of cancer of the liver and of the urinary system are quite plausible given that arsenic is distributed widely throughout the body by the blood and

excreted primarily in the urine. Excess risk of cancer of the digestive tract from inhaled arsenic may result from the swallowing of arsenic dust and/or transport of arsenic by the blood to the digestive tract from the respiratory system.

In evaluating carcinogenic risk, one must consider cancer response by all routes of exposure as well as information on distribution within the body. Vahter (1983) reported that arsenic, absorbed from the gastrointestinal tract or the lungs of experimental animals, is transported by the blood and distributed widely throughout the body. Chen and Chen (1988) reported that arsenic appears to have a similar distribution to the lung, liver, and kidney in experimental animals whether the exposure be by inhalation or ingestion.

Arsenic is unique in that ample data exist to demonstrate that it is carcinogenic in humans via inhalation and ingestion routes of exposure. That this is the case is not particularly surprising because as, previously indicated, arsenic is known to be absorbed by both inhalation and ingestion with similar distribution in the body. The observation that arsenic is carcinogenic by both routes of exposure focuses on an important issue for the risk assessment of other metals, however. Other metallic compounds (e.g., nickel,

cadmium, and hexavalent chromium), while known to be carcinogenic by inhalation, have been studied very little or not at all by the ingestion route of exposure. Nickel, cadmium, and hexavalent chromium, like arsenic, are absorbed by both ingestion and inhalation. Recently, Zhang and Li (1987) reported that stomach cancer mortality was increased in an area of China where there was known to have been hexavalent chromium pollution of the water supply for the previous 25 years. Thus it seems prudent, from a public health perspective, that these metallic compounds should be considered as having the potential to be carcinogenic by both routes of exposure while noting that inherent potency, route absorption differences, or the lack of adequate bioassay testing may explain the failure to observe carcinogenic activity.

Although the arsenic unit cancer risk for gastrointestinal cancer, estimated from the Lee-Feldstein study and presented in this paper, is about four times less than that calculated for the lung cancer response, it is of a magnitude that should be of concern. Dose-response estimates for urinary tract and skin cancer from arsenic inhalation should also be attempted if the data are available.

5. CONCLUSIONS

From the discussion presented here, we draw the following conclusions:

1. Inhalation exposure to arsenic increases the risk of gastrointestinal and urinary tract cancer, as well as lung and skin cancer.
2. As an assumption that favors public health protection, carcinogenic risk from a substance should not be considered route-specific until adequate testing can validate a route-specific response.
3. The unit-risk estimate for gastrointestinal cancer from inhaled arsenic presented here is of concern and should be further investigated.

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